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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 43

Application Number: 08/932834
Filing Date: 09/18/97
Appellant(s): Porubek et al.

Stephen A. Bent
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 4/25/2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct, except that it fails to note that all of the claims are in fact rejected.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief fails to actually recite the status. Specifically, the papers of 5/27/99 and 7/14/99 were not entered; the paper of 7/14/99 was entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because, for reasons set forth below, the examiner believes that the reasoning applies equally well to composition as to compound claims.

(8) Claims Appealed

A substantially correct copy of appealed claim appears on pages 1-13 of the Appendix to the appellant's brief. The minor error is as follows: Claim 9 is given in its original form; but in fact has been twice amended. The claim appears correctly in paper 20 ½, the amendment of 4/18/97 which was entered when the continuation case was filed.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 2, 4, 6, 7, 9, 10, 12-13, 15-16, 17-21, 23-27 are rejected under 35 U.S.C. 112, paragraphs 2, as the claims fail to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

Claims 1, 2, 4, 6, 7, 9, 10, 12-16, 17-21, 23-27 are rejected 35 USC 112, paragraph 1 for lack of enablement, in terms of how to use.

The Indefiniteness Issues:

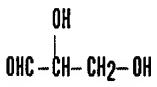
1. The Misdrawn Formula

A part of formula II is drawn wrong. At the left side of Formula II, as it appeared in the specification and original claims was: $(CH_2)_n$. There was nothing wrong with this. Appellants for no reason switched this to: ${}_n(H_2C)$. The subscript n has been switched to the front. The examiner is at a loss to understand why Appellants insist on placing the n in the wrong position when it was placed in the right position in the specification (see page 4, structure II). In a chemical formula, a subscripted numeral appears after the thing which it counts. This is a rule without exception. Thus, in $(CH_2)_3$, the 2 counts the number of hydrogens and the 3 counts the number of methylenes, and the numeral appears always after the thing that it counts. Appellants have not presented any reason why this was done, nor have

they tendered an amendment to fix it. The Appeal Brief discusses "the leading bond" but that is not the problem; the Formula II structure correctly has bonds before and after the $_n(H_2C)$ group. The Appeal Brief says that "the two are equivalent", but that is simply not so. The subscripted numeral counts what comes before it, and in this case, there is nothing to count before the n except the purine nucleus itself, which is not intended. As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous." This rendition is not "correct". (This applies to all claims except 14)

2. The Impossible Carbohydrate Moieties

The carbohydrate moieties added to claim 1, which are choices for R_4, make no sense, because they are supposed to form esters, but cannot; chemically, it is impossible. Appellants are unable to explain what they mean. These appear in the Appendix, page 2, lines 6-10. To use a simple example, the fifth one is "glyceraldehydyl". Glyceraldehydyl is as follows:



Which H is to be removed to make the moiety? Is it one from the OH, and if so which one? Is it from a C, and if so, from the aldehyde carbon, a secondary or tertiary carbon? The response in the Appeal Brief simply makes no sense. The claims language states that the group must be "attached by an oxygen atom ... by an ester linkage" This is not a problem for the

first R4 choice, the "amino acid", which by its very nature is an acid and thus can form an ester with the C* atom, nor is it a problem for the last R4 choice (the OX(R5)m), which must have one R_5 as O and is it thus automatically an ester. But for glyceraldehydyl and all the other carbohydrate moieties, which are all alcohols, these can be linked via an oxygen, but such a compound, e.g. C*-O-CH2CH(OH)CHO would be an ether, not an ester (ether linkage underscored). And Appellants have stated explicitly (paper 37, page 7, last sentence) that ethers are not intended, but esters are. Thus, the "esters" in the claim is not a typographic error. The examiner has repeatedly asked Appellants to just draw out the structure with e.g. glyceraldehydyl (or any of the aldehydes) so one can see what is intended, but Appellants have refused to do this. Instead, Appellants just say, "The artisan will understand, accordingly, the nature of the contemplated molecules". But if Appellants cannot draw the molecule, neither can the skilled artisan. Instead, the Appeal Brief says that one of ordinary skill in the art can form ester by reacting alcohols with acids. Of course this fact is true, but there is no how-to-make rejection. But there is no acid function here to react with the glyceraldehyde alcohol to form an ester. The e.g. glyceraldehyde is an alcohol, but the piece that it hooks up with, the C* is not an acid. The Appeal Brief says, "once converted to their corresponding acids" -- but there is no "conversion" here. There is just the glyceraldehydyl moiety, which is the moiety derived from the removal of H from glyceraldehyde. The problem is, there is no H which, when removed and the moiety is attached to C* will give an ester.

There are also two other problems with this list. What is "ribolucosyl"? The term "glucosidyl" is a broad one with unclear scope, and may embrace others on the list. (This applies to all claims except 13-14)

3. The Term"carboxylic acid moiety" is Indefinite

The term (Claim 6, 4th line) "carboxylic acid moiety" is indefinite. This is a substituent. A carboxylic acid would be something like benzoic acid, or glycine. A moiety is a radical derived by the removal of a H from the molecule. But a) what acids are intended, and b) where is the H removed from? The Appeal Brief is completely silent on this issue. For example, in benzoic acid, removal of a H from the ring would produce the -Ph-COOH group, i.e. the carboxyphenyl group. Removal of the H from the acid end would produce -OC(O)Ph i.e. the benzoyloxy group. There is no way of knowing whether Appellants intend one, the other, or possibly both. With glycine, H_2NCH2COOH, the H could be removed from the C, from the COOH or from the amino group. Are all three intended? Further, one has no idea what sorts of acids are intended. (This applies just to Claim 6)

The Enablement Rejections

4. How to Use Lisofylline

The claims lack enablement in terms of how to use. The compounds in this case, as the Appeal Brief notes, hydrolyze to the corresponding alcohol (i.e. to the compound where R_4 = OH), and in particular, to lisofylline, as the specification notes at page 5, line 35-36. Thus, the claims are drawn to prodrugs of lisofylline. Lisofylline has been studied for many years; it is

one of those "promising" compounds that skilled scientists have not been able to get to actually work. That was true when the case was filed; it is still true. That constitutes prima facie evidence that one of ordinary skill in the art will not be able to get these compounds to work without undue experimentation. It must be emphasized that this is not a rejection under 35 USC 101. Despite repeated statements in the Appeal Brief, the examiner does not assert that lisofylline "has no utility" or "itself is useless". The argument rather is that one of ordinary skill in the art has not been able to get lisofylline to actually work despite much research, and therefore it is clear that undue experimentation is required in such a case. It is particularly instructive to note that nowhere in the entire discussion of this matter in the Appeal Brief is there any mention of what these compounds, or lisofylline, actually do. The closest Appellants come is a reference to the Paradise declaration which the Appeal Brief states (paragraph bridging pages 8-9) "demonstrate that lisofylline is indeed useful for something." What that "something" might actually be, is left unstated.

The declaration is not persuasive. The declaration presents conclusions without supporting facts, and as such is it is it entitled to little or no weight, cf. *In re Etter*, 225 USPQ 1, 6; *In re Grunwell*, 203 USPQ 1055, 1059; *In re Buchner*, USPQ2d 1331; *In re Chilowski*, 134 USPQ 515,521; *In re Brandstadter*, 179 USPQ 286, 293-294, *In re Thompson*, 192 USPQ 275; *Ex parte George* 21 USPQ2nd 1058, 1062. Specifically, with regard to APPENDIX B (the first APPENDIX B, i.e. the Margolin paper), declarant says, "initial clinical trials were conducted, which bore out its therapeutic usefulness at this level." But this

statement, and hence this declaration, is it not credible, because it is directly contradicted by the reference itself. The reference describes a large randomized trial to determine the ability of lysofylline to solve a specific problem, i.e. that IL-2's toxicity limits the amount of it that you can use in treating certain cancers. The last paragraph of the abstract says that lysofylline "did not alter the toxicities of high dose i.v. IL-2 sufficiently to impact the overall dose density of IL-2." The copy of the reference provided to the PTO highlights isolated possible promising findings, but that does not change the fact that the study failed to do what is it set out to do. Thus, page 570 says, "Specifically, LSF [lisofylline] did not permit the administration of more IL-2 and did not substantially alter the toxicity of a fixed dose of IL-2." Moreover, this failure was not an isolated fluke. Page 571 notes that "Other clinical studies attempting to modify the toxicities mediated by IL-2 and other inflammatory cytokines have also been disappointing." This study was, in effect, one more try to get lisofylline to combat the toxicity of IL-2, so that patients could be given higher doses of IL-2. Indeed, the paragraph bridging columns of page 571 strongly suggests that the goal may not be achievable at all. Is it says that "it is likely that some if not all of the phenomena responsible for the multiorgan toxicities ... depend on the same biochemical pathways responsible for the antitumor effects." Thus, disrupting the toxicity of IL-2 would then disrupt the desired effect as well. The last sentence of the abstract suggests that success may require a higher dosage, a more potent agent than lysofylline or the addition of some additional "modulating agents" to the trials. This is clear evidence that more than routine experimentation remains to be done. Even after all these studies, those skilled in

the art still hadn't figured out how to get lisofylline to work. Thus, while the declaration says (paragraph 7) that "a clinician could, via routine clinical procedures, select a suitable dosing scheme" that statement is clearly not consistent with the suggestion in the paper that this massive, multicenter study might well have failed because a dose too low was chosen. If selecting a dose is it so routine, why would the experimenters in the study have suggested that the dose might have been wrong?

There was also an APPENDIX B (second), C and D, which appear to be slides. It is impossible to tell what they are based on, or to what degree the declarant relied on them. APPENDIX E appears to be the abstract of some oral presentation. It is unclear what to make of this because the abstract does not come to any conclusions, since both some positive specific and negative overall language is reported. The paper appears to identify subpopulations which may benefit, but unless the study set out to determine if that subpopulation was more amenable to the drug, that is not necessarily significant. It appears that there was only one treatment arm, and that arm did not differ from placebo. Appellants were told that it would be most helpful in overcoming this rejection if Appellants would supply the published paper corresponding to APPENDIX B (second), C, D or E, assuming that the paper reaches a positive conclusion. This was not done. APPENDIX B (second), C, D or E were not included on the PTO 892 as there is not enough information to cite these, and APPENDIX B (second), C, and D do not appear to be publications but slides.

All of the above analysis appeared in Paper 35 (7/29/99). But the Appeal Brief simply states, "By submitting the Paradise declaration, appellants have gone beyond what is required...." Appellants appear to be of the view that mere submission of the document is enough.

On page 6 of the Appeal Brief, Appellants refer to Examples 22-25 as providing further guidance, without giving any specifics. In paper 26, Appellants had stated that "Example 25 provides treatment of dogs." Treatment of what? The dogs were not treated for anything. No determination was made of the effect of the drug upon the dog. This is no more than a pharmacokinetic study to determine what plasma levels of lisofylline were achieved. The examiner agrees that the compounds tested are prodrugs for lisofylline, so administration of the compound will produce plasma levels of lisofylline, but this does not teach how to use.

Related to this is the lack of useful daily dosage information. Two ranges are set forth on page 9, lines 3-5. The first is 0.1 to 1000 mg/kg, a 10,000 fold range. The second is .001 to 40 mg/kg, a 40,000 fold range. No explanation is given as to why two rather different ranges are given. This is clearly not a case of a broad range and a preferred one, since each range had material in it that the other does not. Further, such ranges are so broad as to be of no practical value; cf. In re Gardner, 166 USPQ 138.

The Appeal Brief on page 5 notes that the first is only an "oral administration" and the second is the generic "administration" which is actually "a typographical error ... it should read "non-oral" administration." This "typographical error" theory, presented for the first

time in the Appeal Brief, is completely speculative. There is no evidence that this is so. In fact, Appellants earlier presented a totally different theory. In paper 8, page 8, second paragraph, Appellants stated that the .001 to 40 mg/kg was "a single administration dose" whereas the 0.1 to 1000 mg/kg was a "daily" dosage.

Appellants also argue on page 3 of the Appeal Brief that one set of claims 1, 2, 4, 6, 7, 9, 10 and 12-14 should be treated separately from 15, 18-21 and 23-27 because compound claims are treated "differently from claims that recite a therapeutic utility." This is confused. No claims recite any sort of therapeutic utility. The rejection applies equally well to claims which have just compound, and claims which have compound plus carrier. There are no method claims of any sort.

Appellants cite *Cross vs Iizuka*, 224 USPQ 739. But the facts were very different there. Cross had a specific enzyme, the inhibition of which was considered in the art to be useful per se for the treatment of asthma. Further, this was bolstered by the fact that structurally related compounds showed the same utility in vitro and in vivo. Determining the correct dosage could be done "without inventive skill or undue experimentation", so that under these circumstances, an in vitro test "may establish a practical utility". Appellants appear to be reading the decision as saying that any sort of in vitro test automatically establishes enablement. The decision says nothing of the sort, and indeed cautions, "Every utility question ... must be decided on its own factual circumstances." In that case, the in vitro test did provide a reasonable correlation to

actual activity. Here, by contrast, it is clear that the art was nowhere near as advanced as it was in *Cross vs Iizuka*, so a different result is appropriate.

Indeed, the facts here are closer to those of Hoffman v. Klaus, 9 USPQ 2d 1657, 1660: "We find no evidence before us here that one skilled in the art at the time the tests were performed would have been reasonably certain that merely because CP-57,850 inhibited the production of collagenase in the in vitro test, it had practical utility. There is no evidence that there was a reasonable correlation between tests and the treatment of arthritis or for any other useful purpose." The two decisions taken together make it clear that these circumstances must be approached individually, on the factual basis of what is known at the time. Here, the examiner has presented evidence that the skill level in this art was not such that one could go from simple tests to practical utility. The various tests establishing the basic properties of lisofylline have been done, but converting those results to practical utility has just not been accomplished. (This applies to all claims)

5. Ethers Don't Hydrolyze

There is a second enablement issue arising directly from point 2. The only thing that moieties such a glyceraldehydyl can form are ethers, and ethers will not hydrolyze. It is understood that Appellants don't actually intend ethers, but that is all the claim language will provide. (This applies to all claims except 13-14)

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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June 12, 2000

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